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Comparing Health Outcome Differences Due to Drug Access: A Model in Non-Small Cell Lung Cancer

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Executive summary

As policy-makers examine a range of options to address concerns about high drug prices in the United States, many are giving renewed attention to the differences in prices between the US and ex-US countries, and are considering deploying coverage and payment tools used in ex-US countries (e.g., cost-effectiveness analysis) to control costs. In this context, it is increasingly important to understand whether ex-US models of drug access hold implications for patient outcomes if they were applied in the US.

Our analysis indicates that, if the access models representing five ex-US comparator countries (Australia, Canada, France, South Korea, and the United Kingdom) were to replace the actual US access conditions between 2006 and 2017, aggregate survival gains (i.e., gains in life years) due to innovative medicines would have been cut in half for US patients diagnosed with locally advanced and metastatic NSCLC. This reduction in health gains is due to the access delays experienced by patients in other countries compared to patients in the US.

This study quantifies the population health impact in the US of introducing non-US models of drug access to an American patient population with locally advanced or metastatic non-small cell lung cancer (NSCLC) between 2006 and 2017. The model simulates the lifetime health outcomes of the target patient population under the actual US access landscape vs. five additional scenarios where US access conditions are replaced by those in the five comparator countries (i.e. characterized by the respective reimbursement approval delays and coverage gaps).

Under each alternative access scenario, the model controls for differences in regulatory approval timelines between the US and other countries. The population health impact of transposing alternative access models to the US is therefore driven by differential rates of coverage and delays in effective first date of reimbursement of the therapies in question.

Model outcomes indicate that American patients diagnosed with locally advanced and metastatic NSCLC between 2006 and 2017 have gained 201,700 life years in total due to access to innovative medicines. They would lose half of this survival benefits if they were living in the other countries.

Moreover, significant discrepancies remain between the access conditions of different countries, with the Australian system leading to the biggest drop in life years at -74% compared to the default US system.

Lastly, a large majority of the life years gained can be attributed to the non-squamous patient population. On a per capita basis the non-squamous population improved their overall survival by 73% due to innovative medicines, compared to 10% improvement in the squamous population. This speaks to the importance of continued investment in the research and development of precision medicines targeting underserved patient subgroups.

Background

Lung cancer is the leading cause of cancer-related mortality in the US and has become the number one killer among cancers worldwide. NSCLC is the most common form, accounting for approximately 85% of all cases.[1] It is often detected at advanced stages - close to 70% of patients with lung cancer

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[1] American Cancer Society, "What Is Non-Small Cell Lung Cancer?" https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html, accessed December 13, 2018

present with locally advanced or metastatic disease at time of diagnosis.[2] Five-year survival rates depend on disease staging. Across all stages, the average rate for lung and bronchus cancer is 18.6%.[3] Among patients in whom the disease has metastasized, the five-year survival rate is less than 5%.[4]

The treatment landscape in NSCLC has improved significantly in the last decade due to development of biomarker-driven therapies that target specific patient populations. These advances have been driven by increased understanding of cancer biology, which has revealed new therapeutic strategies. While great strides have been made and important new treatment options for NSCLC have emerged, access to these treatments varies internationally. Individual countries, shaped by unique reimbursement policies and coverage decision-making frameworks, differ in the time points at and extent to which new treatments are reimbursed.

Many countries utilize aggressive cost-containment strategies targeting pharmaceuticals and, as a result, therapeutic options available to patients in the US do not always become available to patients in other markets – or do so with considerable delay. Even where new therapy options are eventually funded, Health Technology Assessment (HTA) timelines, and associated decision-making and listing procedures, may significantly delay the time at which patients in other countries first gain effective broad-based access.

This study aims to quantify the population health impact of introducing non-US access models to an American patient population with locally advanced or metastatic NSCLC, using a Markov cohort model approach.

Research Methodology

Overview

The Comparative NSCLC Health Outcomes Model estimates how varying access to medicines policies can impact health outcomes in locally advanced or metastatic NSCLC across five comparator countries (Australia, Canada, France, South Korea and the UK) versus the US.

The model comprises a base case which simulates health outcomes in the US, and five additional scenarios where US access conditions are replaced by those in the other markets (i.e. characterized by the associated access models). These scenarios provide insights into the impact on US patients of replacing US access conditions to NSCLC therapies with access conditions in other countries. Population health outcomes include mortality and total life years.

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[2] Riess J, "Shifting Paradigms in Non-Small Cell Lung Cancer: An Evolving Therapeutic Landscape," AJMC, December 2013, https://www.ajmc.com/journals/supplement/2013/ace015_dec13_nsclc-ce/ace015_dec13_nsclc-ce_reiss_s390to97

[3] National Cancer Institute, Surveillance, Epidemiology, and End Results Program, Cancer Stat Facts: Lung and Bronchus Cancer, https://seer.cancer.gov/statfacts/html/lungb.htmlm accessed December 13, 2018

[4] Ibid.

Model structure

Structurally, the model is composed of four submodules: epidemiology, therapies, access, and disease pathway. (Exhibit 1)

- The epidemiology module generates NSCLC patients (relying on US SEER incidence data) between 2006 and 2017, based on disease stage and subtype (please see additional details below under Model Inputs).

- The therapies module defines the individual molecules and classes of drugs accessible in each country, as well as each of their approved indications. The model focuses on innovative pharmacological treatments indicated for stage IIIb and/or IV NSCLC, including the latest generation of chemotherapies, drugs targeting specific tumor mutations (such as EGFR and ALK), and immunotherapies. The effectiveness of these treatments is represented by their impact on patient overall survival (OS) and progression free survival (PFS), as derived from published pivotal randomized clinical trial results, drug labels, and HTA submissions.

Exhibit 1 Model schematic

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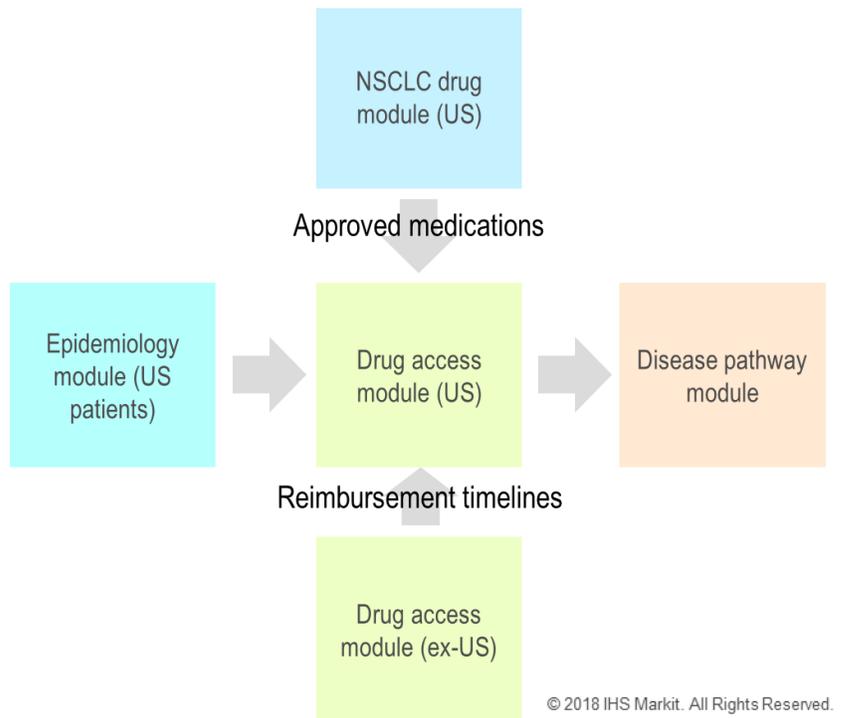
- The access module defines the time points of reimbursement approval in each country, dates of any early access schemes (not sponsored by industry), and US market share assumptions for each class of therapy.

- Finally, the disease pathway module houses transition probabilities among three Markov states (stable disease, progressed disease and death) for each therapy. (Exhibit 2) Treatment responses such as complete response, partial response and stable disease are all grouped under the "stable disease" state. To be consistent with the follow-up schedule of most NSCLC clinical trials, patient transitioning occurs according to three-week cycles. Even though the incident patient population includes those diagnosed from 2006 to 2017, the disease pathway module simulates

Exhibit 2 Disease progression pathway

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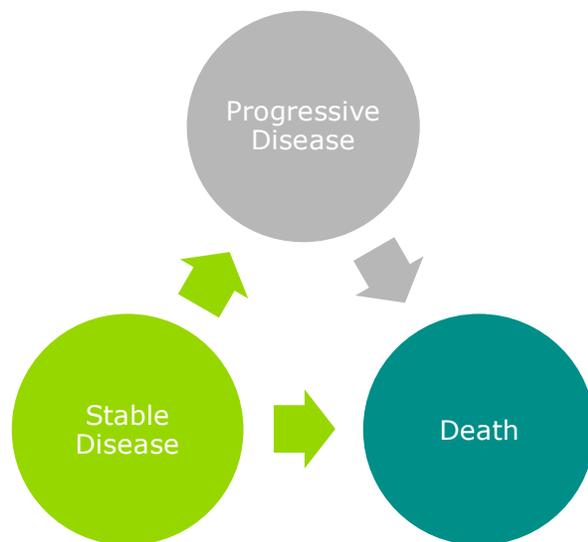
until 2021 (with no incident patients between 2018 and 2021) to cover the life time of all patients.

Patient access

The US NSCLC patient population is subject to the US access timeline in the model base case, as well as the timelines in other countries under alternative scenarios. Therapies are allocated to patients based on lines of treatment, histology (squamous or non-squamous), and US market share, which inherently reflects patient preference and potential off-label usage.

The market share for US patients between 2014 and 2015 was derived from Barclay's research.[5] US market share before 2014 was extrapolated based on the approval time of each drug, with the assumption that market share increases linearly once reimbursement status is obtained (one month after FDA approval) until it reaches the 2014 level. Access timelines in all countries are reinitialized to time of regulatory approval to control for the impact of any difference in regulatory processes.

Exhibit 3 Modeling differential access timelines

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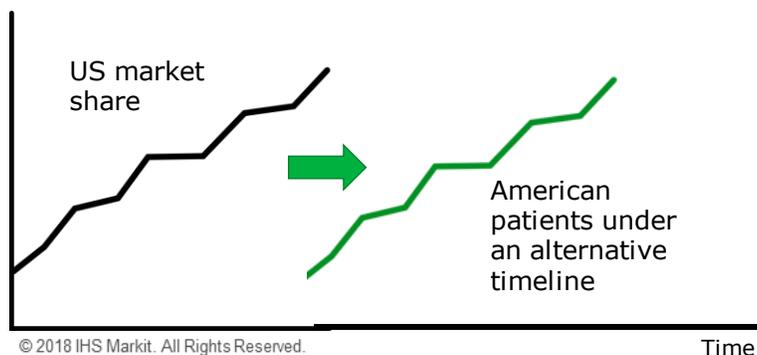
As shown in Exhibit 3, the delay between drug access timelines in other markets and the US is calculated in the model and used to shift US market share accordingly. For example, if a country gains effective access (i.e. reimbursement) six months after the US, the US market share will then be shifted later in time by six months to reflect access timelines in that country.

Model Inputs

Epidemiology

To populate the model, US incidence data for stage IIIb and IV NSCLC were combined. Because median survival of patients at these stages of disease is shorter than one year, annual incidence for these populations was assumed to be the same as prevalence.

Crude incidence rate data for cancer of the lung and bronchus were extracted from one of the Surveillance, Epidemiology, and End Results (SEER) databases [6] using SEER*Stat software.

Histologic subtypes were selected by International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) criteria, and American Joint Committee on Cancer (AJCC) TNM staging criteria were also used to filter the eligible population.

Access Frameworks

For each of the ex-US country scenarios, an access landscape was characterized based upon the regulatory, HTA and reimbursement approval procedures in place in each country. This involved a mapping of decision points from regulatory approval to first effective reimbursement, so as to

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[5] Barclays, Immuno-Oncology and Emerging Market Dynamics, https://www.slideshare.net/LesleyBailey1/alphaimpactrx-barclays-oncology-webinar-1-dec-2015, December 1, 2015, accessed December 13, 2018
[6] ("SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (2000-2013) <Katrina/Rita Population Adjustment>"

identify access delays and gaps in coverage relative to the US base case scenario. Data on regulatory and reimbursement approvals for each therapy, in each indication, were gathered from the country-specific sources outlined below.

Australia

Regulatory approval dates were drawn from the Therapeutic Goods Administration (TGA) website. Public Summary Documents of Pharmaceutical Benefits Advisory Committee (PBAC) meetings were consulted to identify HTA outcomes, while the Schedule of Pharmaceutical Benefits was consulted to identify date of first effective reimbursement.

Canada

Regulatory approval dates were drawn from the Health Canada Notice of Compliance (NOC) database. For drugs launched after 2011, filing and decision dates (including Provincial Funding Summaries) associated with the pan-Canadian Oncology Drug Review (pCODR) were consulted. For dates of first effective reimbursement for drugs not reviewed by pCODR, Ontario was chosen as a representative province. The websites for the New Drugs Funding Program (NDFP), Exceptional Access Program (EAP) and Ontario Drug Benefit (ODB) program were consulted to obtain or estimate dates of first effective reimbursement. For drugs on the NDFP, personal communications with a senior pharmacist at Cancer Care Ontario confirmed certain listing dates. A literature review was also conducted to validate certain dates and fill in gaps. In a few cases, where submissions for drugs with NOCs were not yet made to pCODR by the study cut-off time (end of 2017), date of first effective reimbursement was assumed to follow the median delay of other therapies.

France

Regulatory approval dates were drawn from the assessment history on each medicine's profile on the European Medicines Agency (EMA) website. Dates of first effective reimbursement were identified from consultation of relevant entries in the *Journal Officiel*. Date of first reimbursement was assumed to be the day following publication in the *Journal*, unless otherwise specified. In a few instances, due to lack of entries in the *Journal*, the median delay between *Haute Autorité de Santé* HTA decision and *Journal* listing was used to fill in gaps in first effective reimbursement date for therapies otherwise known to be approved for reimbursement and accessible.

South Korea

Regulatory approval dates were drawn from the medicines database maintained by the Ministry of Food and Drug Safety. The website of the health insurance regulator, the Health Insurance and Review Assessment (HIRA), was consulted in order to identify dates of first effective reimbursement as specified in amendments to the list of items for prescribing to cancer patients (암환자에게

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UK

Regulatory approval dates were drawn from the assessment history on each medicine's profile on the EMA website. The website of the National Institute for Health and Care Excellence (NICE) was consulted for decision dates for all relevant Single Technology Appraisals. Such decisions become binding across the National Health Service in England after three months. The archive for the list of drugs accessible under the Cancer Drugs Fund (CDF) was also consulted. If a drug first appeared on this list prior to recommendation for baseline funding by NICE, this date was taken as date of first
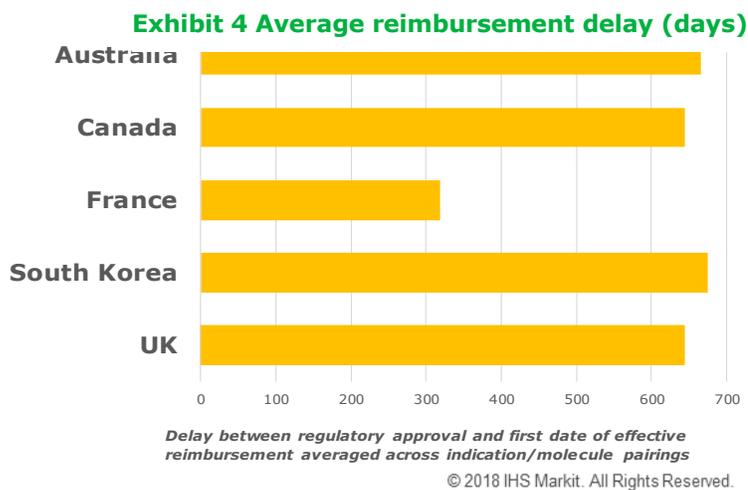
effective reimbursement. Because the CDF was nationalized from April 2013, this was the earliest date that broad-based access was assumed for medicines entered early into the scheme.

US

Regulatory approval dates were drawn from the Food and Drug Administration (FDA) website. Centers for Medicare and Medicaid Services (CMS) recognized antineoplastics as one of six "classes of clinical concerns" and required part D to cover "all or substantially all drugs" in this category.[7] Additionally, time from approval to launch in the US was estimated to be 17 days for oncology drugs.[8] Hence, dates of first effective reimbursement were assumed to be one month following the approval date.

Access Outcomes

The resulting access delays (in terms of number of days between regulatory approval and date of first effective reimbursement) for each molecule/indication pairing form one part of the access module for each ex-US country. In Exhibit 4, it can be seen that, averaged across such pairings, there is a delay of between 600 to 700 days (average delay 589 days) in most countries, in contrast to the 30-day delay assumed to operate in the US market. France forms an exception with a delay of approximately 318 days.
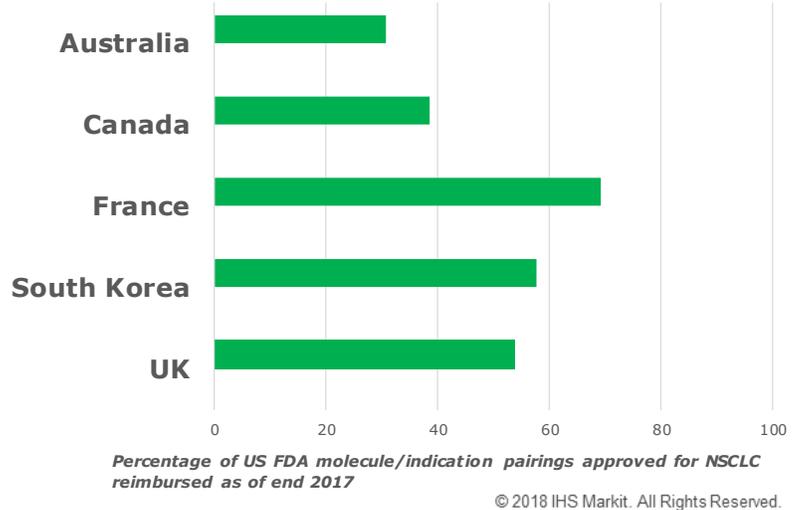
Exhibit 4 Average reimbursement delay (days)

Delay between regulatory approval and first date of effective reimbursement averaged across indication/molecule pairings

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[7] Centers for Medicare and Medicaid Services, Medicare Prescription Drug Benefit Manual, https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R2PDB.pdf, July 18, 2008, accessed December 27, 2018
[8] Mycka, J, Dellamano R, Lobb W, Dalal N, et al., Regulatory Approval to Patient Access, an Evaluation of EU5 and US National Timing Differences, ISPOR 6th Asia-Pacific Conference, Beijing, September 6-9, 2014, http://www.m2econ.com/publicationdocs/2014/PHP62.pdf

Access delays form only one part of the access module for each ex-US country, with the second component defined by extent of coverage across all potential molecule/indication pairings, relative to regulatory approvals in the US. While ex-US average access delays generally converge within a narrow range, Exhibit 5 underscores that there is more variation with regards to extent of coverage, indicating marked differences in the absolute number of molecule/indication pairings approved for reimbursement across countries. By the end of 2017, extent of coverage ranges from

Exhibit 5 Extent of reimbursement coverage (%)

Percentage of US FDA molecule/indication pairings approved for NSCLC reimbursed as of end 2017

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approximately 31% of such pairings in Australia to 69% in France (average coverage 50%). This input, alongside the access delays associated with molecule/indication pairings having secured coverage, form the basis of each access module and hence ex-US access scenario, as transposed to the US population as part of the modelling exercise.

Outcomes and Discussion

Subjecting American patients with locally advanced or metastatic NSCLC (Stage IIIb and IV) to the access timelines of Australia, Canada, France, South Korea, and UK invariably led to a considerable decrease in patient overall survival. American patients who were diagnosed with locally advanced and metastatic NSCLC between 2006-2017 are estimated to have gained 201,700 life years in total due to innovative medicines. If the drug access timelines from the 5 comparator countries were introduced in the same period in lieu of the existing US reimbursement timelines, the increased survival benefits for US patients would have been cut nearly in half. (Exhibit 6)
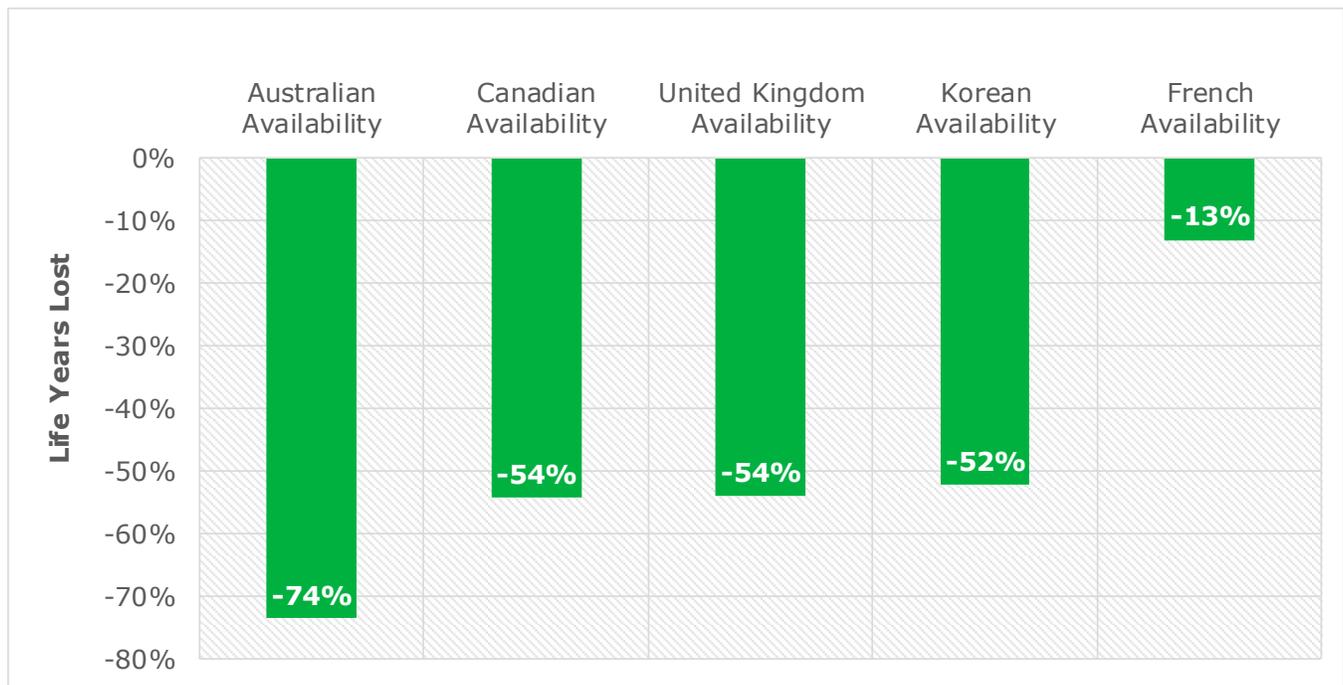
Exhibit 6 Life years gained due to innovative medicines under alternative access timeline

Estimated Treatment Gains from Innovative Medicines in the United States — 201,700 Life Years

Estimated Average Treatment Gains Under International HTA — 101,920 Life Years

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Specifically, significant discrepancies remain between the access conditions of different countries. American patients would benefit the least under the Australian access timeline by losing 74% of the

population health benefit. Even though the European Medicine Agency (EMA) makes all centralized market authorization decisions, there are significant differences among the reimbursement processes of various European countries. For example, American patients could keep less than 50% of the benefit of innovative medicines if subject to drug availability and access timelines of the UK. In contrast, if the American drug access landscape were to change to that of France, American patients would lose 13% of the life years gained due to innovative medicines. This is in line with other studies comparing delays in patient access due to HTA. A prominent study published in European Society of Medical Oncology (ESMO) compared the duration from EMA approval to HTA decisions for 47 drugs across 77 solid tumor indications. It revealed that the median delay was two to three times longer in England (405 days) and Scotland (384 days) compared to France (118 days).[9]

Exhibit 7 Life years lost if subjecting American NSCLC patients to alternative drug availability and access timelines (US = 0%)

Finally, cancer histology also plays an important role in determining population health outcomes. Out of the 201,700 life years gained from access to innovative medicines, 194,900 (97%) life years were derived from patients with non-squamous NSCLC and only 6,800 life years (3%) were from the population with squamous NSCLC. On a per capita basis, because most innovative medicines were approved for non-squamous NSCLC, patients with this subtype lived 73% longer while those with squamous NSCLC only lived 10% longer. This speaks to the heterogeneity within cancer patient populations, and shows that medicine innovations can disproportionally benefit certain patient subgroups. On a related note, the discovery of epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements has helped identify patients who are more likely to benefit from a certain drug.[10] By highlighting both the great potential and unmet need, our study supports the importance of continued investment in the research and development of

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[9] https://www.esmo.org/Press-Office/Press-Releases/MCBS-HTA-cancer-drugs-approval-Hwang, October 19, 2018, accessed December 13, 2018
[10] Minguet, F, Smith, KH, Targeted therapies for treatment of non-small cell lung cancer—Recent advances and future perspectives, International Journal of Cancer, 2015, https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.29915

personalized medicines targeting underserved patient subgroups with specific cancer subtypes or genetic mutations.